390

[redacted]

Chief, OD/MS

8 December 1951

Chief, Security Research Staff, OS

Cytomel

1. During the course of recent discussions between representatives of this Agency and Dr. [redacted] and [redacted], the use of a relatively new drug named Cytomel was explained by [redacted], who, as you know, is a well-known psychiatrist and one of the board members of the [redacted] Clinic at the University of [redacted] Medical School and hospitals. Details follow.

2. In discussing the handling of acute alcoholic cases, particularly those who are in delerium or even approaching a serious physical condition, Dr. [redacted] stated that he and his associates have recently been testing cytomel. Dr. [redacted] stated that this drug has had an absolutely amazing effect on the breaking up of DT's and counteracting alcoholic overindulgence. According to Dr. [redacted] this drug, when given in heavy doses, generally intravenously, will break up DT's and alcoholic convulsions or alcoholic embarrassments often in a matter of a few minutes. He cited examples where the drug had been used with startling effect, and Dr. [redacted], who was present, stated that he too had begun use of the drug in acute alcoholic cases. Both doctors stated that this was particularly valuable in situations who are violent and are hallucinating and control is necessary as soon as possible. Dr. [redacted] suggested that this might be of some use to the Agency, suggesting that this could be used as heretofore stated. Agency representatives present at this meeting immediately asked Dr. [redacted] if this drug would have an intense sobering effect which might serve for operational reasons to which Dr. [redacted] replied that it would be definitely useful in that connection and that it should be examined most carefully.

2. Dr. [redacted] stated that Cytomel now comes in apparently capsule form of 5 MCG but that heavy dosages of 25 MCG were being used experimentally. Both doctors suggested that the drug could be used very effectively if placed under the tongue or given rectally, although as mentioned previously in a clinical way it was being used intravenously. When questioned as to whether or not there were side effects, both doctors stated that there were no side effects that had been established.

3. When questioned as to whether the drug could be used as a preventative or a technique for maintaining sobriety even when heavy drinking was required, both doctors were of the opinion that it would probably be highly efficient along these lines.

4. When asked the name of the drug house producing cytomel, Dr. [redacted] believed that it was Ciba and indicated that he would gather literature on the drug and send it immediately to Mr. [redacted] of the Office

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58-50

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of Security.

5. In view of the above, it is the opinion of the Agency representatives who hold the discussion that medical authorities of the Agency should undertake an examination of the properties of this drug with a view toward its possible operational use as outlined. It is suggested that if this drug has such properties and is as effective as indicated by Dr. [redacted] and Dr. [redacted], perhaps it could be made in the form of a "life-saver" or a throat lozenge, which could be carried by an Agency representative in a routine manner and which would not create undue interest if placed in the mouth.

6. Mr. [redacted] will forward any information received on the drug cytomel to your office immediately upon receipt.

[redacted]

58-51

[redacted]

[redacted] M. D.
[redacted] M. D.
[redacted] M. D.
[redacted] M. D.

December 8, 1961

[redacted]
Washington 8, D. C.

Dear Mr. [redacted]:

Enclosed is The New England Journal of Medicine, which contains the article on Intravenous Cytomel. You may make photostatic copies of this article and then return the magazine to me for my files. The I.V. Cytomel works beautifully on cases of acute alcoholism. It is not available as yet for general use.

What you are more interested in is the use of oral Cytomel. This too has brought exceedingly good results in the clearing of acute alcoholism. We generally give a 25 or 50 microgram tablet. Very shortly the person is sober.

Since Cytomel is a thyroid drug, one should not continue on such medication since it will depress the thyroid so much that after five days of continuous medication the thyroid gland is totally depressed. However, with one or two tablets of Cytomel the effect will be minimal.

As I pointed out to you, it may well be that an agent who has to drink to be sociable while on an important assignment could slip a tablet in his mouth after taking several drinks and should be sober within twenty to thirty minutes. Cytomel is supposed to oxidize the alcohol. I believe that this could be an important adjunct to your work. Certainly it is worthwhile to study it further. No doubt you will want to get some qualified specialist in internal medicine to pass his judgment upon it. Make sure, however, he is truly qualified and knows something about the study before passing a decision. I sincerely hope this will be of help to your department.

It was such a very great pleasure to meet with you, Mr. [redacted] and Mr. [redacted] and to discuss our mutual problem. Rest assured should the situation arise again, I will handle it to the best of my ability.

With all good wishes,

Sincerely,

[redacted]

[redacted]

585

THE NEW ENGLAND JOURNAL OF MEDICINE Dec. 29, 1960

INTRAVENOUS TRI-IODOTHYRONINE IN ACUTE ALCOHOLIC INTOXICATION*

Preliminary Report

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WORCESTER, MASSACHUSETTS

THE effect of the thyroid hormone, L-tri-iodothyronine, in rapidly sobering up acutely intoxicated alcoholic patients has been mentioned by Rawson, Koch and Flach[1] and by one of us (M.G.).[2] Since the previous reports pertained to topics other than the management of acute alcoholism, however, the details concerning this mode of treatment were not included. Our current experience with the intravenous use of a preparation of the hormone in the therapy of acute alcoholism — one that employs an objective parameter of changing levels of alcoholic intoxication, serial blood alcohol determinations — has been most impressive. The following report is intended to present, in brief, our findings in 12 patients with acute alcoholism treated intravenously with L-tri-iodothyronine as compared with 8 untreated, acutely intoxicated controls.

MATERIALS AND METHODS

The 20 patients, 14 males and 6 females, were selected at random for this study from the patients admitted to the Alcoholic Ward of St. Vincent's Hospital. The ages ranged from twenty-seven to fifty-eight years. Owing to the limited number of patients with acute alcoholism admitted to the hospital per week and available for study, no attempt was made to match the controls and treated patients by sex, age or approximate size. The random process employed to assign acutely intoxicated patients to the control or treated groups consisted only of withholding or administration of the hormone on alternate weeks during the interval of investigation. Fortuitously, the average value of initial blood alcohol levels for the two groups fell in the same approximate vicinity: 338 mg. per 100 ml. for the treated patients and 321 mg. per 100 ml. for the controls (Fig. 1). Three patients assigned to the control group and 1 assigned to the treated group were excluded from the present data because the initial blood alcohol levels obtained on them were less than 150 mg. per 100 ml. — an arbitrary level generally accepted to indicate definite intoxication.

The majority were known to have chronic alcoholism, with several previous admissions to the hospital for excessive drinking. The solution for intravenous use was prepared from sodium tri-iodothyronine powder.¶ Once dissolved in a solution of pH 10.5 and refrigerated, it will remain stable for approximately five to seven days; it is stable at room temperature for one or two days. A dose of 200 microgm. was selected for all treated patients in this study. Specimens for blood alcohol levels were drawn before and at intervals of two, four and eight hours after administration; specimens were drawn from the controls at the same intervals. The method described by Leifheit[3] was utilized in the chemical determination of blood alcohol concentration, and all specimens were run in duplicate.

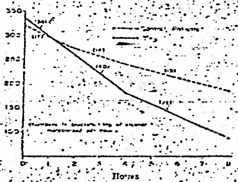

FIGURE 1. *Rate of Decline of Blood Alcohol in Treated and Control Alcoholic Patients.*

T_3 = tri-iodothyronine.

In addition to the decline in blood alcohol, the following clinical criteria were employed to assess change toward sobriety: ability to give a rational history in patients initially in a stuporous state; ability to walk a straight line; ability to hold arms and fingers outstretched without a noticeable tremor; and disappearance of the odor of alcohol from the breath (as estimated by several observers).

RESULTS

As shown in Tables 1 and 2, the mean rate of metabolism of alcohol — as expressed in terms of the decline in blood alcohol in milligrams per 100 ml. per hour (Widmark's beta) — was 32.1 mg. in the treated patients, as compared with 15.0 mg. in the controls. The decline was twice as rapid in the former. The fall in blood alcohol had particular therapeutic value in patients such as A.L. and R.H., whose initial

*[illegible]

†Research associate, [illegible], St. Vincent's Hospital.

‡[illegible], St. Vincent's Hospital.

§[illegible] associate, St. Vincent's Hospital.

¶[illegible] by Smith Kline and French Laboratories, Philadelphia.

58-5

levels of blood alcohol approached the lethal limits of intoxication.[4] Figure 1, a composite curve of the serial blood alcohol levels in both treated and untreated patients, shows that the greatest increment in decline occurred in the first two to four hours in the treated patients.

A statistical analysis of these data, employing the Fisher "t test" for unpaired data,[5] showed the results for the effect of the hormone on decline of blood alcohol to be highly significant ($t = 8.6$; $p < 0.001$).

As judged clinically, the great majority of patients were considered to be relatively sober within two hours of the intravenous injection of tri-iodothyronine by the criteria previously mentioned. The disappearance of the alcoholic odor from the breath within this two-hour period was particularly striking and uniformly observed. In comparison, among the controls, an alcoholic odor persisted on the breath for six to ten hours.

The ability to obtain a rational medical history within one or two hours in patients who have consumed large quantities of alcoholic beverages and are admitted to the hospital in a stuporous or semicomatose state is probably the greatest practical advantage of this method of therapy. The following case history is illustrative:

TABLE 1. *Effect of Tri-iodothyronine on Rate of Blood Alcohol Decline in 12 Treated Patients.*

Patient	Blood Alcohol Level: Before Treatment	2 Hr. after Treatment	4 Hr. after Treatment	8 Hr. after Treatment	Rate of Blood Alcohol Decline
	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml./hr.
F.Mc.	320	260	120	45	34.4
T.Mc.	240	165	100	—	33.0
P.G.	410	345	299	160	31.2
I.C.	355	250.5	170	35	37.8
A.L.	400	340	216	140.5	30.7
R.H.	435	363	261	169	33.3
H.S.	320	295	230	167	25.6
O.G.	200	100	25	14	24.4
S.P.	342	310	278	101	30.5
A.W.	378	320	260	125	31.6
A.W.	323	240	159	24	36.0
E.O'L.	138	116	30	12	23.2
Averages	326	260	181	82.5	Mean 32.1; S.D. ±3.22

A.W., a [illegible]-year-old truck driver, was admitted to the Alcoholic Ward in a semicomatose state. The intern on duty in the [illegible] room stated that he had been brought in by police [illegible] after being found unconscious in the street. [illegible] or painful stimuli [illegible] from bruises on the face and [illegible], and a strong [illegible] of alcohol on the breath. Physical examination was [illegible]. No relatives who might supply the doctor in attendance with information about the presence of any prior head illness could be found. The police officers could not say whether or not the patient had been hit by a car or had sustained any head injuries. The vital signs were all normal with the exception of a blood pressure of 170/110.

On arrival on the Alcoholic Ward, blood was drawn for [illegible] alcohol and other blood chemical findings, and 200 micrograms of tri-iodothyronine was administered by vein. Within 1 hour the patient was able to sit up in bed and was fully oriented. He was then able to give a lucid history, which confirmed the impression of alcoholic intoxication and was negative for trauma. He also mentioned that he was hypertensive and usually ran a systolic blood pressure of 220. Within 90 minutes of the intravenous injection he was able to walk a straight line and to hold out his hands without obvious tremor. Four observers could no longer detect the odor of alcohol on the breath. He subsequently slept in short naps until approximately 8 hours after admission to the ward, when he complained of being shaky and tremulous. The blood alcohol had then fallen from an initial value of 378 to 125 mg. per 100 ml. He was then given 100 mg. of promazine intramuscularly, which alleviated the symptoms. The remainder of the 24-hour hospital stay proceeded uneventfully.

TABLE 2. *Data in Untreated Control Patients.*

Patient	Blood Alcohol Level: at 0 Hr.	at 2 Hr.	at 4 Hr.	at 8 Hr.	Rate of Blood Alcohol Decline
	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml.	mg./100 ml./hr.
H.B.	220	180	143	120	12.3
F.T.	380	318	320	273.5	13.3
R.N.	370	330	306	245	15.6
L.G.	255	254	227	144	18.9
C.T.	420	382	345	200	17.5
A.M.	325	256	260	205	15.0
J.H.	190	162	130	83	13.4
T.H.	368	331	302	254	14.2
Averages	321	287	254	200	Mean 15.0; S.D. ±2.21

($T = 8.6$; $p < 0.001$)

Discussion

An admirable review by Harger and Hulpieu[6] of numerous studies concerning the natural rate of decline of blood alcohol levels in both acutely intoxicated human beings and laboratory animals has shown that the average value for Widmark's beta is 15 mg. per 100 ml. per hour, with a range of 12 to 23 mg. These authors further state that, to their knowledge, no drug that is without harm to the body and can significantly increase the disappearance rate of alcohol from the blood has as yet been found — including such present day therapeutic measures as glucose-insulin infusions and various vitamins for parenteral administration. Although the present data are derived from a limited number of cases, they demonstrate a fairly consistent increase in the rate of alcohol metabolism to double the control values in patients receiving tri-iodothyronine intravenously, as well as a prompt sobering-up effect, which can be observed clinically.

390

[illegible] attempting to compare the action of the hormone on alcohol metabolism when given by various routes of administration are presently in progress. Although a limited experience with tri-iodothyronine given sublingually by [illegible] and ourselves shows this route to be effective, [illegible] therapy can only be given to the co-operative alcoholic patient. The experience of Catz[7] and others with oral administration has been disappointing, and in view of the unpredictable rate of absorption, this route is not recommended.

It is to be emphasized that our present findings indicate that intravenous or sublingual administration of tri-iodothyronine is merely a useful adjunct to the presently available methods of treatment of acute alcoholism, such as parenteral infusion of fluids, vitamins and tranquilizers, and not a means unto itself. We believe, however, that it has a unique effectiveness in the not uncommon situation in which a comatose or semicomatose patient with a strong odor of alcohol on the breath is taken to the hospital by ambulance or police escort and is unable to give a clear medical history. Since several hours usually elapse before the attending physician can determine whether or not the condition is due to alcoholism alone or is complicated by serious medical, surgical or neurologic catastrophe, an effective means by which one can rapidly sober up such a patient sufficiently to obtain a first-person history of events is highly desirable. In contrast, the administration of sedatives or tranquilizers does nothing to accelerate the sobering-up processes, and may actually hinder them.

Among the 12 patients given 200 microgm. of tri-iodothyronine intravenously and followed closely for any change in vital signs or untoward responses, no side reactions or evidence of toxicity has been observed. Freedom from any untoward reactions has likewise been seen in an additional 10 patients given the hormone intravenously, in 18 patients given 100 to 200 microgm. sublingually and in several dog experiments.[3] Considering that 200 microgm. of the hormone is the equivalent of approximately 0.4 to 0.5 gm. (6 to 8 gr.) of desiccated thyroid and that an excess of circulating thyroid hormones is known to have a detrimental influence on cardiac function, both by a direct toxic effect on the myocardium and by potentiating the action of the catechol amines, we exercised great caution in attempting to exclude any patient with known coronary-artery disease from the treated group. Adrenal insufficiency is likewise a second contraindication to thyroid-hormone therapy. A possible exception, which may be considered a side reaction to therapy, has been the observance of moderate tremulousness and [illegible] in 1 patients six [illegible]

[illegible] state of rapid alcohol withdrawal rather than to the administered thyroid hormone. In the future an attempt to verify this hypothesis will be made by intravenous injection of alcohol at the time such symptoms as tremulousness and nervousness occur.

One patient with active delirium tremens manifested by auditory and visual hallucinations was likewise treated with tri-iodothyronine intravenously. Since the blood alcohol on admission was reported to be 25 mg. per 100 ml. the effect of the drug on the rate at which alcohol was metabolized could not be determined. The hallucinations disappeared, however, within one hour of the injection, and did not reappear.

Finally, one can only speculate about the precise site of action of the hormone in accelerating the natural pathways of alcohol metabolism. Considering that numerous studies by Hetzel, Charnock and Good[?] and others have been unable to detect a significant effect of intravenously administered tri-iodothyronine on tissue metabolism earlier than eight hours after injection, it seems probable that the acceleration of alcohol metabolism is not dependent in full on a general enhancement of body metabolism but more probably is a direct effect on the hepatic enzyme systems that convert alcohol to acetaldehyde. This, of course, remains to be proved. In fact, studies by Wolff and Wolff[10] have demonstrated an inhibiting action of thyroid hormones on yeast alcohol dehydrogenase in vivo, so that (if the theory outlined above is correct) other pathways of alcohol detoxification, such as the catalase reaction, may be involved.

Summary and Conclusions

An investigation of the use of thyroid hormone L-tri-iodothyronine in the management of acute alcoholism has shown this agent to have a prompt sobering-up action when given intravenously in a total dosage of 200 microgm. Among 12 patients who received this treatment and were compared with 8 untreated, acutely intoxicated controls, the following results were obtained: the rate of blood alcohol decline averaged 15.0 mg. per 100 ml. per hour in the controls and 32.1 mg. per 100 ml. per hour in the treated patients; patients given the hormone were judged to be clinically sober and able to give a rational medical history within two hours after the injection; the odor of alcohol was undetectable on the breath two hours after treatment, although it persisted for six to ten hours in the untreated controls. Intravenous therapy appears to be a valuable adjunct in the treatment of acute alcoholism, particularly when such a patient is admitted to the hospital in a stuporous or semicomatose state secondary to severe intoxication and is unable to give a coherent medical

5825

390

[illegible] about the value of intravenous injection of triiodothyronine in the routine management of acute alcoholism, our preliminary studies have shown a fair uniformity of response in blood alcohol curves and clinical assessment of sobriety. It is hoped that this report will prompt others to verify our findings.

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MYCOTIC ENDOCARDITIS FOLLOWING INTRACARDIAC OPERATIONS*

Report of Four Cases

Bong Hak Hyun, M.D., D.Sc. (Med.),† and Fred C. Collier, M.D.‡

PHILADELPHIA

MYCOTIC endocarditis, especially after cardiac surgery, has seldom been observed.[1-7] Bacterial endocarditis complicating recovery from such operations, however, is not uncommon,[8-12] is usually disclosed by blood culture and is often responsive to appropriate antimicrobial therapy. No distinction between mycotic and bacterial endocarditides can be made on clinical grounds. Therefore, investigation of postoperative fever calls for procedures that will identify fungi as well as bacteria.

It would seem that mycotic endocarditis is increasing.[13,14] If true, this would not be surprising, considering the ubiquity of fungi and the rapidly expanding field of cardiac surgery. Within a nine-month period, 4 cases of endocarditis due to *Candida albicans* were observed in two of the hospitals associated with the University of Pennsylvania School of Medicine, and they are summarized in this communication. The first case has been reported in detail elsewhere,[8] but, because of the rarity of reports of this condition, it is included in brief along with the other 3 reported for the first time.

Case Reports

Case 1. A 40-year-old man (P.H.P. 170101) was admitted to the Presbyterian Hospital in Philadelphia, where the diagnosis of mitral insufficiency was established. Circumferential suture of the mitral ring was performed 7 days later, without incident. No antibiotics had been given preoperatively.

On the 12th postoperative day fever and chills developed, and the blood culture was positive for *Staphylococcus aureus.* Penicillin therapy was instituted. When the oral route was substituted for the parenteral route of penicillin administration at the end of 8 weeks fever promptly recurred, and blood cultures were again positive for *Staph. aureus.* Despite resumption of parenteral administration the patient's condition deteriorated; it improved somewhat on ACTH, cortisone and desoxycorticosterone acetate. Again, substitution of the oral for the parenteral route of penicillin administration resulted in prompt reappearance of *Staph. aureus* in the blood stream, and the patient died 105 days after operation.

Autopsy revealed thrombotic material containing both *C. albicans* and *Staph. aureus* adherent to the circumferential suture, the posterior half of which was lying free in the left atrioventricular cavity.

Case 2. A 37-year-old man (H.U.P. 081230) was admitted to the Hospital of the University of Pennsylvania suffering from aortic stenosis. After direct catheterization of the left side of the heart hemopericardium developed. Sixteen days later the patient underwent aortic valvulotomy by finger fracture. Preoperatively, he had been given penicillin and streptomycin for 2 weeks.

The immediate postoperative course was marked by fever, the temperature ranging from 99 to 102°F. Replacement of penicillin and streptomycin by tetracycline was accompanied by more severe pyrexia, and the original regimen was re-established, with the addition of chloramphenicol. Multiple blood cultures were negative until the 30th postoperative day, when blood and iliac-marrow cultures were positive for *C. albicans.* Massive antibiotic therapy, utilizing amphotericin B, penicillin, bacitracin and nystatin, was then instituted. Five days after the 1st positive blood culture, Osler's nodes and conjunctival petechiae developed. Nystatin and actidione were given intravenously to the patient, who died 35 days after the 1st positive blood culture and 2 months after the operation.

The significant autopsy findings included cardiac hypertrophy, partially alleviated stenosis of the aortic valve, which was covered by fungus-laden vegetations, and a fistula between the right sinus of Valsalva and the right atrium (Fig. 1). Mycotic emboli were present in the right iliac artery, the kidneys and the segmental pulmonary artery to the left upper lobe.

Case 3. A [illegible]-year-old man (H.U.P. 073131) was admitted to the Hospital of the University of Pennsylvania [illegible]

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585